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Oleic Acid Based Emulgel for Topical Delivery of Ofloxacin

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ABSTRACT

The objective of the present study is to formulate and evaluate ofloxacin emulgel. Emulgel formulations of ofloxacin were prepared using different concentrations of gelling agent's Carbopol-940 and Xanthum gum. Tween-80 and span-80 were used as emulsifiers and propylene glycol as a humectant in the preparation of emulgel. The effect of the concentration of gelling agent on the drug release from the prepared emulgel was investigated. The compatibility study was conducted using Fourier-transform infrared (FTIR). The formulated emulgel was characterized by their physical appearance, pH determination, viscosity, spreadability, drug content, microbial test and in vitro diffusion study. FTIR indicated that the drug and excipients used in the study are compatible with each other. All the prepared formulations showed acceptable physical properties, homogeneity, consistency, spreadability, viscosity, and pH value. Drug release from all the formulations depended upon the concentration of the polymer used. As the concentration of Carbopol 940 increased the spreadability and drug release was found to be decreased. Emulgels formulated with oleic acid gave a much higher release rate of ofloxacin than emulgels formulated with liquid paraffin. The release of drug from all the emulgels prepared followed Zero-order kinetics. The linear Higuchi plots indicated that the drug release from all the emulgels prepared followed diffusion kinetics. Emulgel formulated with oleic acid exhibited greater flux when compared with those formulated with liquid paraffin. The formulations were found to be stable during stability testing. It can be concluded that Carbopol 940 and oleic acid are recommended for the formulation and preparation of Ofloxacin emulgels for topical drug delivery.

Key words: Ofloxacin, Emulgel, Spreadibility, Zone of inhibition.

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INTRODUCTION

Emulgels are the topical drug delivery systems that are formed by combining gels and emulsions in a suitable ratio. Gelling agents are used to converting emulsion into an emulgel[1,2]. Oil-in-water systems are used to solubilize lipophilic drugs whereas water-in-oil systems are used to encapsulate hydrophilic drugs. Emulsions are thermodynamically unstable and hence their stability can be increased by converting into emulgel. Emulgels present several advantages like pleasant appearance, greaseless nature, easy spreadability, washable, thixotropy, emollient action, nonstaining and proponed shelf life.[3,4]

Ofloxacin is fluoroquinolone with broad-spectrum antibacterial activity. Ofloxacin is active on both actively dividing as well as dormant bacteria. The mechanism is by inhibition of bacterial DNA gyrase. Ofloxacin has a wide range of antibacterial activity for the treatment of systemic as well as a local infection. The half-life of Ofloxacin is 6-7 hrs. Ofloxacin is slightly soluble in water and methanol. It belongs to BCS class II drug with low solubility and high permeability. The objective of the present work is to formulate and evaluate ofloxacin emulgel using different concentrations of Carbopol 940 and Xanthum Gum.

MATERIALS AND METHODS

Ofloxacin was a gift sample from PVS Labs, Vijayawada. Carbopol 940, Oleic acid, Span 80, Tween 80 and propylene glycol 400 and other chemicals were procured from commercial sources.

Drug – Excipient Compatibility Study

Drug – excipient compatibility studies of Ofloxacin and formulated emulgels were determined using FTIR Spectrophotometer (BrukerATR Alpha –e, Germany) in KBr disc. [5]

Preparation of Emulgel

Ofloxacin emulgels were prepared as per the formula is given in Table-1. Ofloxacin (1%) was dissolved in

oleic acid and stirred for 10 min on a magnetic stirrer at 400-500 rpm. Span 80 was added in with stirring on a magnetic stirrer at 400- 500 rpm. The aqueous phase was prepared by dissolving Tween 80 and PEG 400 in an aqueous phase with stirring using a magnetic stirrer at 400-500 rpm. Oil and aqueous phase were heated separately at 70 -80°C. Then the oil phase was mixed with an aqueous phase with continuous stirring. Carbopol gel was prepared by dispersing Carbopol 940 in purified water with constant stirring at a moderate speed. The gel was obtained by neutralizing the dispersion with triethanolamine and pH was adjusted to 5- 7. The obtained emulsion was mixed with gel in a 1:1 ratio to get an emulgel using homogenizer.

Table: 1. Formulation of Ofloxacin Gel and Emulsion

Ingredients (%)	**OF1**	**OF2**	**OF3**	**OF4**	**PF1**	**PF2**	**PF3**	**PF4**
	Formulation of gel							
Carbopol 940	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0
Propylene glycol	2	2	2	2	2	2	2	2
Methylparaben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Ingredients (%)	**OE1**	**OE2**	**OE3**	**OE4**	**PE1**	**PE2**	**PE3**	**PE4**
	Formulation of emulsion							
Ofloxacin	1	1	1	1	1	1	1	1
Span 80	6	6	6	6	6	6	6	6
Oleic acid	10	10	10	10	-	-	-	-
Liquid paraffin	-	-	-	-	10	10	10	10
Tween 80	6	6	6	6	6	6	6	6
Propylene glycol	10	10	10	10	10	10	10	10
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Propylparaben	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Ethanol	2	2	2	2	2	2	2	2

Evaluation of Emulgel

Emulgels were evaluated for clarity, color, homogeneity, drug content, pH and viscosity. pH was determined with a digital pH meter at room temperature. Viscosity was determined by using Brookfield's viscometer (spindle No.4)[6]

Spreadability

Spreadability was determined by an apparatus suggested by Mutimer et al. The apparatus was modified and it consists of a wooden block with a pulley at one end. A rectangular ground glass plate was fixed on the block. Gel (about 2 g) was placed on the lower plate and was sandwiched between lower and upper glass plate having the same dimensions, provided with the hook. 500 mg weight was placed on the top of the two plates for 5 min to expel air and to get a uniform film of gel. The excess of the gel was scraped off. The upper plate was subjected to a pull of 50 g. Time (sec) required by the upper plate to cover a distance of 10 cm was noted. The spreadability was calculated from the following equation. Shorter the time interval better the spreadability.

$S = M \times L / T$

Where, S = Spreadability, M = weight tied to upper slide, L = length of the glass slide, T = time taken for plates to slide the entire length (sec).

***In-vitro* Diffusion Study**

In-vitro Diffusion Study was carried out in Franz diffusion cell using the egg membrane. The egg membrane was placed between the donor and receptor compartment. 1g of the gel was placed in the donor compartment. The entire surface of the membrane was in contact with the receptor compartment containing 25 ml of phosphate buffer of pH 6.8. The contents of the donor cell were agitated using magnetic stirrer at 50 rpm and temperature maintained at 37±1°C. 2 ml were withdrawn at intervals of 15, 30, 60, 120, 180, 240, 300, 360, 420 and 480 min and was replaced with equal volume of fresh phosphate buffer of pH 6.8 each time. Samples were evaluated measuring their absorbance at 287 nm.[7.]

Release Experiment / Model dependent method

Drug release from emulgels was analyzed as per zero order, first order, and Higuchi's kinetic models[8]

Zone of Inhibition

This technique is used to study the bacteriostatic activity of the compound. Zone of Inhibition produced by ofloxacin emulgels was determined using the strains of Bacillus subtilis and Escherichia coli in eight agar plates. In the present study agar medium and cup plate technique was used. The overnight grown culture of Bacillus subtilis and Escherichia coli was inoculated into the sterilized agar media plates. In each agar plate, the single-cup was produced and gels were filled into the cups. As a standard, distilled water was used. All eight agar plates were kept for incubation for 24 hrs. After 24hrs the plates were observed and the zone of inhibition was measured[9].

Stability study

Stability study was carried on the optimized formulation to assess the stability of Emulgel after storage using a stability chamber. The emulgel formulation was packed in a clean and dry vial and stored under the accelerated condition of 40°C ± 2°C/75% ± 5% RH for a period of 3 months. Samples were withdrawn at an interval of 1, 2, 3 months for accelerated stability conditions. Samples were evaluated for physical appearance (visually inspected for any change in color and appearance), drug content and viscosity [10-12].

RESULTS AND DISCUSSION

The drug excipient compatibility od ofloxacin with excipients is determined by using FTIR spectra. The spectra are given **Fig.1-3.** Ofloxacin exhibited characteristic peaks as shown in **Figure 1**.

The following peaks were observed in FTIR spectra of ofloxacin.

PROMINENT PEAK (cm^{-1})	REASON
3050 & 3000	Due to stretching vibrations of hydroxyl group and inter molecular hydrogen bonding: presence of –NH stretching vibrations.
2700	Presence of $-CH_3$ of methyl group.
1750-1700	Presence of acidic carbonyl C=O stretching
1650-1600	Due to N-H bending vibration of quinolones.
1550-1500	Corresponds to CH_2 of aromatic ring.
1450-1400	Due to stretching vibrations of CH_2; Presence of methylene group in benzoxazine
1400-1350	Due to bending vibration of hydroxyl group.
1250-1200	Due to stretching vibrations of oxo group.
1050-1000	This strong absorbance peak is due to C-F group.
900-800	Due to plane bending vibrations of double bond 'enes' or =CH group.

The spectrum of drug and excipients mixture did not show any major change in drug peaks. Hence it can be concluded that there was no significant interaction between drug and excipients used in the study.

Fig. 1:FTIR spectra of Ofloxacin

Fig. 2: FTIR Spectra of Ofloxacin Emulgel Containing 1% of Carbopol 940

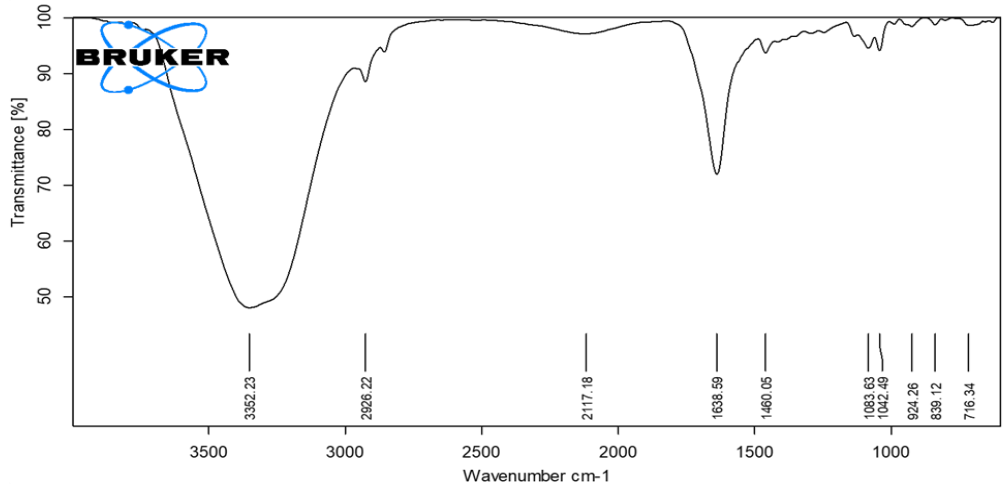
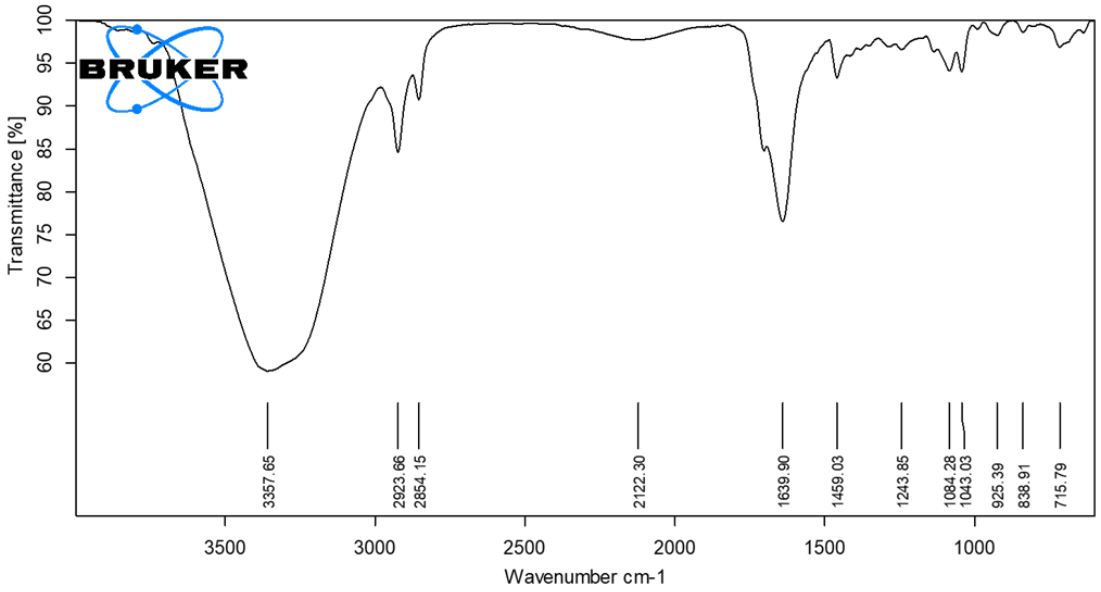


Fig. 3: FTIR Spectra of Ofloxacin Emulgel Containing 2% of Carbopol 940



Evaluation of emulgel

Emulgels were found to be yellowish, white viscous creamy preparations with a smooth, homogeneous texture and glossy appearance with no grittiness and phase separation. Emulgels prepared were found to be stable and there was no physical separation of emulsion from emulgel. The results were in Table 2. The prepared emulgels were evaluated for pH, spreadability, viscosity, drug content and values are depicted as in Table 3 and Figs.4 & 5. pH of the prepared emulgel formulation was found in the range of 5.5–6.8 which is an acceptable range for the topical preparations. Formulations containing 0.5% Carbopol 940 did not show results for some of the evaluation parameters. OF1 and PF1 formulation showed poor gelling property due to the low viscosity of 0.5% of the Carbopol-940. The spreadability of the formulation was found in the range of 23.87–85.55 g.cm/s. The spreadability studies indicated that as the concentration of the gelling agent increases spreadability decreases. The viscosity of the various emulgels was found in between the range of 11500–22100 cps. Ofloxacin emulgels were found to be more effective against Bacillus subtilis (gram +ve bacteria) when compared with E.coli (gram –ve bacteria).The results are given in Table 4 and Fig.6 & 7.As the concentration of Carbopol increases, the viscosity of emulgel increases and the zone of inhibition decreases. The viscosity and zone of inhibition studies indicated that the diffusion of ofloxacin from various emulgels is dependent on the concentration of Carbopol used.

Table: 2. Physical Characteristics of Ofloxacin Emulgel

Formulation	Colour	Phase separation	Grittiness
OF1	Yellowish White	No	None
OF2	Yellowish	No	None
OF3	White	No	None
OF4	Yellowish	No	None
PF1	White	No	None
PF2	Yellowish	No	None
PF3	White	No	None
PF4	Yellowish	No	None

Table 3: Evaluation Parameters of Emulgel Preparations

Batch	OF1	Of2	OF3	OF4	PF1	PF2	PF3	PF4
pH	6.8	5.8	6.4	6.2	5.5	6.0	5.6	5.8
Spreadability (g.cm/s)	85.55	55.55	33.11	23.87	80	46.55	31.28	18.23
Viscosity (cps) Speed at 12 rpm	11500	15750	20750	21100	12500	14750	19750	22100
Drug content (%)	97.64	98.22	98.57	98.80	97.64	94.31	96.31	95.28

Fig. 4: Viscosity of Ofloxacin Emulgel Preparation

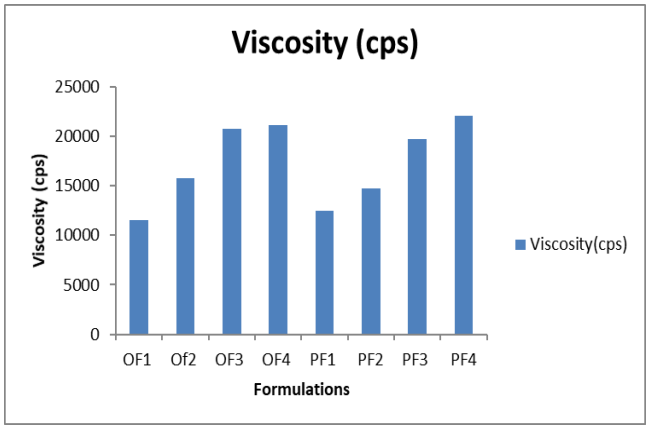


Fig. 5: Spreadability of Ofloxacin Emulgel Preparation

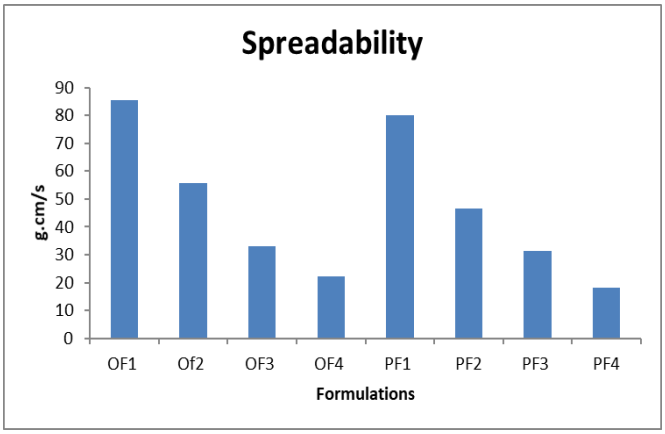


Table 4: Zone of Inhibition Obtained from Ofloxacin Emulgel Formulation

Zone inhibited by emulgel formulation		
Formulation	**Bacillus subtilis (cm)**	***E. coli* (cm)**
OF1	2.2	1.4
OF2	1.9	1.2
OF3	1.4	1.1
OF4	1.2	1.0
PF1	1.9	1.2
PF2	1.7	1.1
PF3	1.8	1.0
PF4	1.5	0.9

Fig. 6: Zone of Inhibitions of Ofloxacin Emulgel Preparation

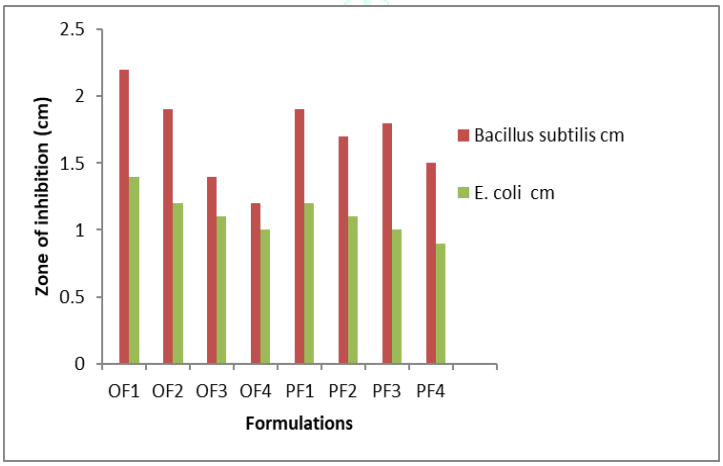
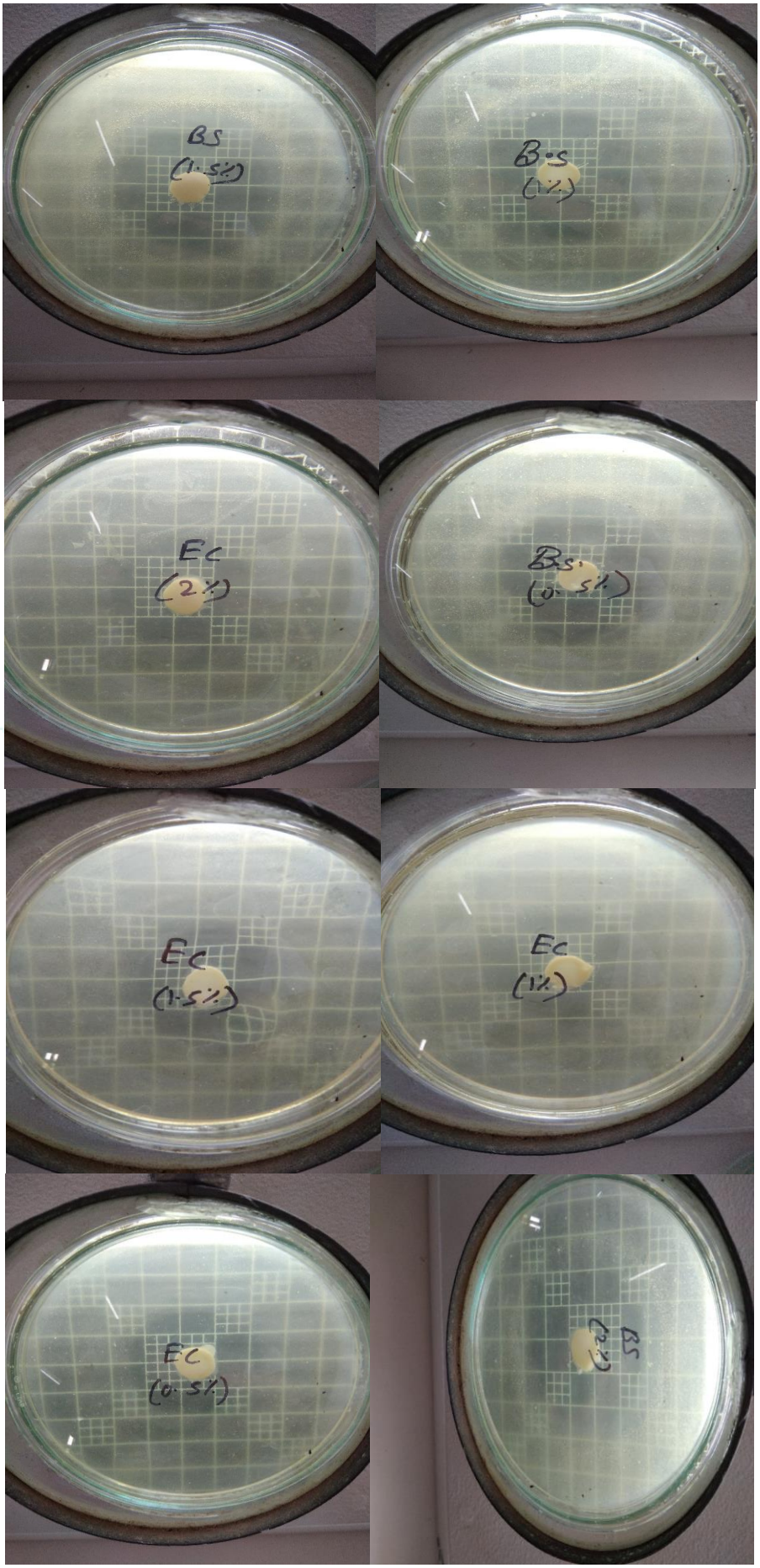


Fig. 7: Zone of Inhibitions of Ofloxacin Emulgel Preparations



***In vitro* drug release study**

Release of drug from the formulation was dependent on the nature and concentration of polymer used. Formulations with Carbopol 940 showed the drug release in order of F1>F2>F3>F4. As the concentration of Carbopol 940 is increased the release rate of drug was found to be decreased. The drug release profiles are given in Fig.8 & 9. Emulgels formulated with oleic acid gave much higher release rate of ofloxacin than emulgels formulated with liquid paraffin. From the release profiles it can be concluded that the carbopol 940 emulgel with low concentration of polymer F1 shows maximum release. Emulgels formulated with xanthum gum exhibited fungal growth and were not found suitable for formulation of emulgels. Hence carbopol 940 was found to be better polymer than xantham gum for formulation of emulgels. The release kinetics based on coefficient of determination (R^2) indicated that the release of drug from all the emulgels prepared followed zero order kinetics. The linear Higuchi plots indicated that the drug release from all the emulgels prepared followed diffusion kinetics. The results are given in Table 5. The flux values were in the range of 0.739-1.575µg/cm^2/min in case of oleic acid emulgels and 0.401-1.41µg/cm^2/min in case liquid paraffin emulgels. As the concentration of Carbopol increases the flux decreases indicating that diffusion of drug decreases with increasing viscosity of emulgel. Emulgel formulated with oleic acid exhibited greater flux when compared with those formulated with liquid paraffin.

Fig. 8: In vitro Drug Release Profiles of Ofloxacin Emulgels Prepared using Oleic acid

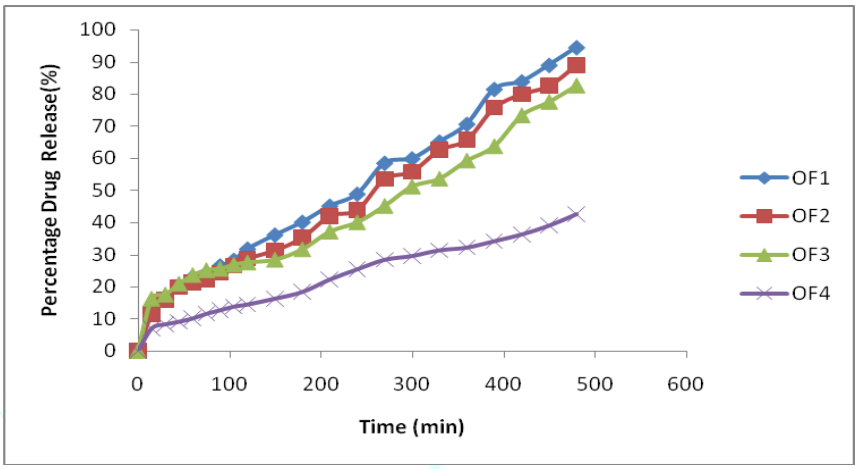


Fig. 9: In vitro Drug Release Profiles of Ofloxacin Emulgels Prepared Using Liquid Paraffin

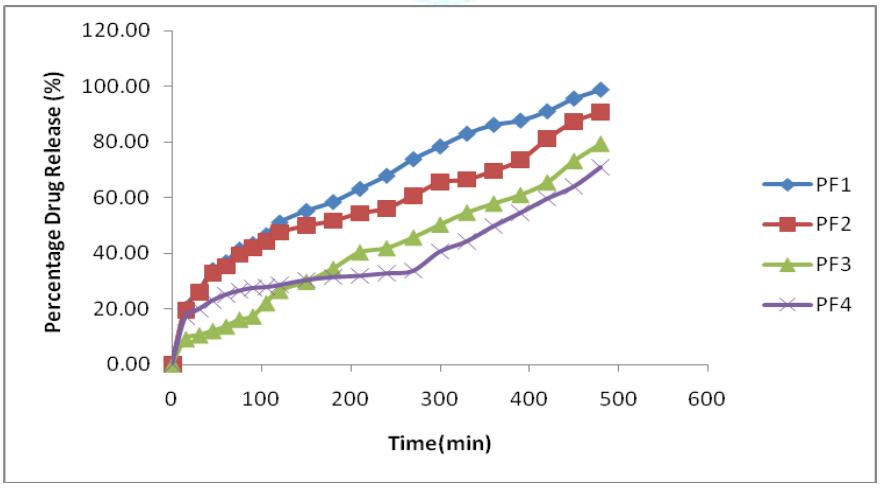


Table 5: Co-efficient of Determination(r^2) Values as per Zero order and First Order Kinetic models

Formulation	Zero order	First order
PF1	0.952	0.936
PF2	0.995	0.971
PF3	0.957	0.949
PF4	0.967	0.931
OF1	0.992	0.994
OF2	0.983	0.948
OF3	0.992	0.947
OF4	0.992	0.936

Stability studies

The formulations PF2 and OF2 were subjected to stability study, for 3 months. Parameters such as physical appearance, pH, viscosity and drug content were found to be stable. No major changes were observed in their parameters, the slight changes were seen which were in acceptable limit ($P<0.05$).

CONCLUSION

A stable, elegant and effective ofloxacin emulgel was developed using carbopol 940 and oleic acid. Ofloxacin emulgel exhibited good in-vitro drug release and viscosity. Emulgel acts as a depot of drug which will release the drug in a controlled manner at the applied site. Hence Carbopol 940 and oleic acid are recommended for the formulation and preparation of ofloxacin emulgels for topical drug delivery.

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